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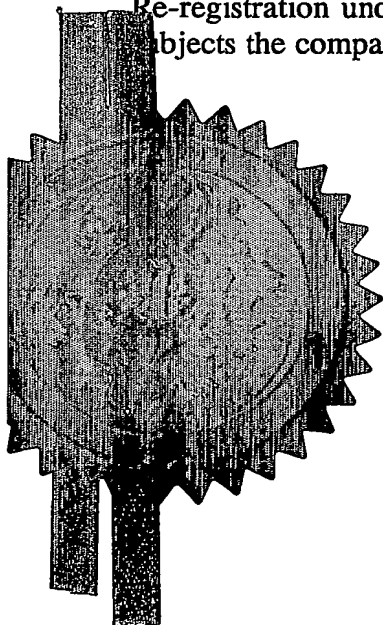
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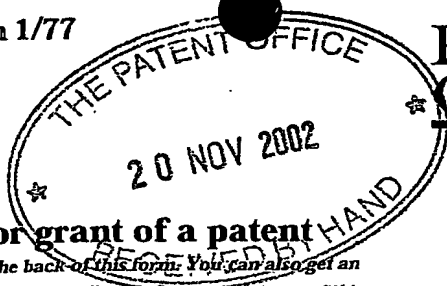


Signed

Stephen Handley

Dated

10 December 2003



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1/77

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1. Your reference	REP0723 OGB	21NOV02 E765111-23 D02890
		P01/7700 0.00-0227131.0
2. Patent application number (The Patent Office will fill in this part)	0227131.0	
3. Full name, address and postcode of the or of each applicant (underline all surnames)	Amedis Pharmaceuticals Limited Unit 209 Cambridge Science Park Milton Road Cambridge CB4 0GZ	
Patents ADP number (if you know it)		
If the applicant is a corporate body, give the country/state of its incorporation	United Kingdom	8025595003
4. Title of the invention	COMPOUNDS AND THEIR USE	
5. Name of your agent (if you have one)	Gill Jennings & Every	
"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)	Broadgate House 7 Eldon Street London EC2M 7LH	
Patents ADP number (if you know it)	745002	
6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number	Country	Priority application number (if you know it) Date of filing (day / month / year)
7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day / month / year)
8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if: a) any applicant named in part 3 is not an inventor, or b) there is an inventor who is not named as an applicant, or c) any named applicant is a corporate body. See note (d))	YES	

Patents Form 1/77

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Claim(s)	1 ✓
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Translations of priority documents

Statement of inventorship and right to grant of a patent (*Patents Form 7/77*)

Request for preliminary examination and search (*Patents Form 9/77*)

Request for substantive examination (*Patents Form 10/77*)

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11. For the applicant
Gill Jennings & Every

I/We request the grant of a patent on the basis of this application.

Signature

Date

20 November 2002

12. Name and daytime telephone number of person to contact in the United Kingdom

R E Perry

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COMPOUNDS AND THEIR USE

Field of the Invention

This invention relates to compounds and their use in therapy.

Background to the Invention

5 Gonadotropin-Releasing Hormone (GnRH) plays a key role in the biology of reproduction. GnRH is also known as luteinizing hormone-releasing hormone (LH-RH).

The GnRH decapeptide (pyro-Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH₂ or p-EHWSYGLRPG-NH₂) is formed in neurons of the medial basal hypothalamus from a larger precursor via enzymatic processing. The peptide is released in a pulsatile manner into the pituitary portal circulation system, where GnRH interacts with high-affinity receptors (7-Transmembrane G-Protein Coupled Receptors) in the anterior pituitary gland located at the base of the brain. Here, GnRH triggers the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), both of which are gonadotropic hormones (gonadotropins). LH stimulates the production of testosterone and estradiol in the testes and ovaries respectively, whilst FSH stimulates follicle growth in women and sperm formation in men. When correctly functioning, the pulsatile release and concentration levels of GnRH are critical for the maintaining of gonadal steroidogenesis and for normal functions of reproduction related to growth and sexual development.

The pituitary response to GnRH varies greatly throughout life. GnRH and the gonadotropins first appear in the foetus at about ten weeks of gestation. Sensitivity to GnRH reduces until the onset of puberty. There is, however, a brief rise during the first three months after birth. Prior to puberty, the FSH response to GnRH is greater than that of LH. Once puberty begins, sensitivity to GnRH increases, and pulsatile LH secretion ensues. Later in puberty and throughout the reproductive years, pulsatile release of GnRH occurs throughout the day, with responsiveness to LH being greater than that of FSH. Pulsatile GnRH release results in pulsatile LH and FSH release and thus testosterone and estradiol release from the gonads. Post-menopause, the concentration of FSH and LH rise, and the post-menopausal levels of FSH are higher than those of LH.

Chronic administration of GnRH agonists and antagonists results in decreased circulating levels of both LH and FSH. GnRH agonists are compounds that mimic endogenous GnRH to stimulate receptors on the pituitary gland, resulting in release of LH and FSH. After a transient rise in gonadal hormone production ("flare" response), the chronic administration of GnRH agonists results in down-regulation of the GnRH receptors. This down-regulation and desensitization results in a reduction in the circulating levels of LH and FSH. In spite of the symptom-exacerbating hormonal flare experienced, GnRH agonists have been the preferred treatment for sex-steroid-dependent pathophysiologies. GnRH agonists have been used to reduce testosterone production, thereby reducing prostate volume in benign prostatic hyperplasia (BPH) and slowing tumour growth in prostate cancer. Such compounds have also been used in the treatment of breast and ovarian cancers.

In recent years, GnRH antagonists have become available for clinical evaluation, and have been shown to have an immediate effect on the pituitary but without the observed flare associated with agonists. Use of GnRH antagonists has been reported for the treatment of ovarian, breast and prostate cancers.

Other uses of antagonists include endometriosis (including endometriosis with pain), uterine myoma, ovarian and mammary cystic diseases (including polycystic ovarian disease), prostatic hypertrophy, amenorrhea (e.g. secondary amenorrhea), and precocious puberty. These compounds may also be useful in the symptomatic relief of premenstrual syndrome (PMS). Antagonists may also be useful to regulate the secretion of gonadotropins in male mammals to arrest spermatogenesis (e.g. as male contraceptives), and for treatment of male sex offenders. GnRH antagonists and agonists have been shown to have utility in treatments where a reversible suppression of the pituitary-gonadal axis is desired.

The presence of GnRH receptors on anterior pituitary cells and several tumour cell types offers the opportunity to develop drugs that act upon receptors to treat both hormone-dependent and hormone-independent cancers.

Conventionally, androgen deprivation has been the most effective systematic therapy for the treatment of metastatic carcinoma of the prostate. The prostate gland requires androgens for normal growth, maintenance, and function. Prostate cancer and benign prostate hyperplasia, however, are common in men and develop in an environment of continuous exposure to androgen. Utilizing a GnRH antagonist to interrupt the pituitary-gonadal axis reduces androgen production and results in tumour growth modulation.

GnRH antagonists may have a direct effect on tumour growth by blocking receptors on the tumour cells. For those cancer types that respond both to sex hormones and to GnRH directly, antagonists should be effective in slowing tumour growth by two mechanisms. Since GnRH receptors are present on many prostate and breast cancer cells, it has recently been proposed that GnRH antagonists may also be effective in treating non-hormone-dependent tumours. Recent literature examples indicate that GnRH receptors are present on a number of cancer cell lines. In particular, prostate, ovarian and breast cancers (see for example Montagnani *et al*, *Arch. Ital. Urol. Androl.* **1997**, 69(4), 257-263; Jungwirth *et al.*, *Prostate* **1997**, 32(3), 164-172; Srkalovic *et al.*, *Int. J. Oncol.* **1998**, 12(3), 489-498; Kottler *et al.*, *Int. J. Cancer* **1997**, 71(4), 595-599.

Available GnRH antagonists have primarily been peptide analogues of GnRH (see, for example, WO93/03058). Peptide antagonists of peptide hormones have some potency but, the use of current peptide antagonists is often associated with problems because peptides are degraded by physiological enzymes and often poorly distributed within the organism being treated. They thus have a limited effectiveness as drugs.

WO00/20358 discloses non-peptide analogues of GnRH.

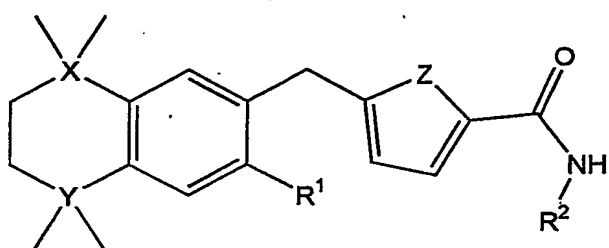
Sila-substitution (C/Si-exchange) of drugs is a relatively recent approach for searching for organosilicon compounds which have beneficial biological properties. The approach involves the replacement of specific carbon atoms in compounds by silicon, and monitoring how the biological properties of the compounds have changed. A review of this approach is provided in Tacke and Zilch, *Endeavour, New Series*, 10, 191-197 (1986).

Summary of the Invention

The present invention concerns small-molecule non-peptide GnRH antagonists that exploit both of the above-described mechanisms of action. Such non-peptide agents may have advantageous physical, chemical and biological properties compared to peptides, and are useful medicaments for diseases such as those mediated via the pituitary-gonadal axis and by directly targeting the receptor on tumour cells.

According to a first aspect of the invention, a compound has the formula

(I)



(I)

wherein

one of X and Y is Si and the other is C or Si;

Z is NR, O or S and R is H or alkyl;

R¹ is H, halogen, alkyl, alkenyl, alkynyl or cycloalkyl; and

R² is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -alkyl-cycloalkyl, -alkyl-heterocycloalkyl, -alkyl-aryl or -alkyl-heteroaryl;

or a pharmaceutically acceptable salt thereof.

Another aspect of the invention is the use of a compound of formula (I) for the manufacture of a medicament for the treatment or prevention of diseases or conditions mediated by GnRH.

Another aspect of the invention is a pharmaceutical composition comprising a compound of formula (I) and a pharmaceutically acceptable diluent or carrier, for use in therapy.

Compounds of the invention are GnRH antagonists and as a consequence may have therapeutic utility in the treatment or prevention of cancer. The compounds may provide better biodistribution and tolerance to

degradation by physiological enzymes, and are thus pharmaceutically advantageous over peptide compounds.

Description of the Invention

5 Certain compounds and combinations of substituents are preferred, in particular see the subclaims.

Preferred compounds of the invention include those wherein R^1 is H or alkyl, preferably methyl or ethyl and/or R^2 is aryl, preferably substituted aryl.

10 The term "alkyl" as used herein refers to an optionally substituted straight or branched chain alkyl moiety having from one to six carbon atoms, including for example, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, pentyl, hexyl and the like. " C_{1-6} alkyl" has the same meaning. The group may be optionally substituted with hydroxy and the like.

15 The term "alkenyl" as used herein refers to an optionally substituted straight or branched chain alkyl moiety having two to six carbon atoms and having in addition at least one double bond, of either E or Z stereochemistry where applicable. This term includes for example, vinyl, 1-propenyl, 1- and 2-butenyl, 2-methyl-2-propenyl etc. " C_{2-6} alkenyl" has the same meaning. The group may be optionally substituted with hydroxy and the like.

20 The term "alkynyl" as used herein refers to an optionally substituted straight or branched chain alkyl moiety having two to six carbon atoms and having in addition at least one triple bond. " C_{2-6} alkynyl" has the same meaning. The group may be optionally substituted with hydroxy and the like.

25 The term "aryl" as used herein refers to optionally substituted aromatic ring systems comprising six to ten ring atoms, and optionally substituted polycyclic ring systems having two or more cyclic rings at least one of which is aromatic. This term includes for example, phenyl and naphthyl. The group may be optionally substituted with the substituents being the same or different in each occurrence and selected from halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxy, silyloxy, amino, nitro, sulfhydryl, alkylthio, amido, phosphoryl, phosphonate, 30 phosphino, carbonyl, carboxyl, carboxamido, alkylsilyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, ketone, ester, heteroalkyl, cyano, guanidine, amidine, acetal, ketal, amine oxide, aryl, heteroaryl, arylalkyl, heteroarylalkyl, carbamate,

hydroxamic acid, imido, sulfonamido, thioamido, thiocarbamate, urea and thiourea.

5 The term "cycloalkyl" as used herein refers to a saturated alicyclic moiety having from three to six carbon atoms and includes for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like. The group may be optionally substituted by any substituent described herein.

10 The term "heterocycloalkyl" as used herein refers to a saturated heterocyclic moiety having from four to seven carbon atoms and one or more heteroatoms selected from the group N, O, S and includes for example azetidiny, pyrrolidiny, tetrahydrofurany, piperidiny and the like. The group may be optionally substituted by any substituent described herein.

15 The term "heteroaryl" as used herein refers to aromatic ring systems of five to ten atoms or which at least one atom is selected from O, N and S and includes for example furany, thiophenyl, pyridyl, indolyl, quinolyl and the like. The group may be optionally substituted by any substituent described herein.

The term "alkoxy" as used herein refers to a straight chain or branched chain alkoxy group containing between one and six carbon atoms, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy and the like. "C₁₋₆ alkoxy" may have the same meaning.

20 The term "halogen" as used herein refers to an atom selected from F, Cl, Br or I.

A compound of the invention may be in a protected form. Compounds of the invention may be chiral. They may be in the form of a single enantiomer or diastereomer, or a racemic mixture.

25 It will be appreciated that where a particular stereoisomer of formula (I) is required, the synthetic processes described herein may be used with the appropriate homochiral starting material and/or isomers may be resolved from mixtures using conventional separation techniques (e.g. HPLC).

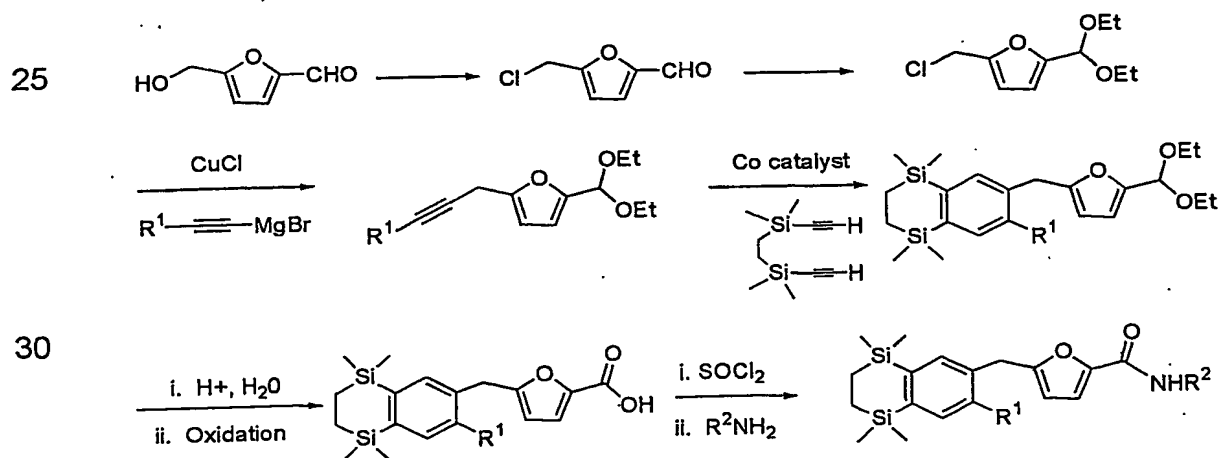
30 Compounds of the invention may be in the form of pharmaceutically acceptable salts, for example, addition salts of inorganic or organic acids. Such inorganic acid addition salts include, for example, salts of hydrobromic acid, hydrochloric acid, nitric acid, phosphoric acid and sulphuric acid. Organic acid

addition salts include, for example, salts of acetic acid, benzenesulphonic acid, benzoic acid, camphorsulphonic acid, citric acid, 2-(4-chlorophenoxy)-2-methylpropionic acid, 1,2-ethanedisulphonic acid, ethanesulphonic acid, ethylenediaminetetraacetic acid (EDTA), fumaric acid, glucoheptonic acid, gluconic acid, glutamic acid, 4-hexylresorcinol, hippuric acid, 2-(4-hydroxybenzoyl)benzoic acid, 1-hydroxy-2-naphthoic acid, 3-hydroxy-2-naphthoic acid, 2-hydroxyethanesulphonic acid, lactobionic acid, n-dodecyl sulphate, maleic acid, malic acid, mandelic acid, methanesulphonic acid, methyl sulphate, mucic acid, 2-naphthalenesulphonic acid, pamoic acid, pantothenic acid, phosphanilic acid ((4-aminophenyl)phosphonic acid), picric acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, terephthalic acid, p-toluenesulphonic acid, 10-undecenoic acid and the like.

Salts may also be formed with inorganic bases. Such inorganic base salts include, for example, salts of aluminium, bismuth, calcium, lithium, magnesium, potassium, sodium, zinc and the like. Organic base salts include, for example, salts of N, N'-dibenzylethylenediamine, choline (as a counterion), diethanolamine, ethanolamine, ethylenediamine, N,N'-bis(dehydroabietyl)-ethylenediamine, N-methylglucamine, procaine, tris(hydroxymethyl)aminoethane ("TRIS") and the like.

As used hereinafter, the term "active compound" denotes a compound of formula (I) including pharmaceutically acceptable salts thereof.

A compound of the invention may be prepared by any suitable method known in the art and/or by the following process.



It will be understood that the process detailed above is solely for the purpose of illustrating the invention and should not be construed as limiting. A process utilising similar or analogous reagents and/or conditions known to one skilled in the art may also be used to obtain a compound of the invention.

5 Any mixtures of final products or intermediates obtained can be separated on the basis of the physico-chemical differences of the constituents, in known manner, into the pure final products or intermediates, for example by chromatography, distillation, fractional crystallization, or by formation of a salt if appropriate or possible under the circumstances.

10 A preferred compound of the invention is *N*-(2,4,6-trimethoxyphenyl)-5-[3,5,5,8,8-pentamethyl-5,8-disila-5,6,7,8-tetrahydro-2-naphthyl)methyl]furan-2-carboxamide.

The activity and selectivity of the compounds may be determined by any suitable assay known in the art.

15 This invention also relates to methods and compositions for the treatment for patients suffering from disorders or diseases which can be attributed to GnRH as previously described, and more specifically, a method of treatment involving the administration of compounds of formula (I) as the active constituents. Accordingly, the compounds of formula (I) can be used in the
20 treatment of disease or conditions associated with GnRH.

As mentioned above, compounds of formula (I) are useful in medicine since they are GnRH antagonists. Accordingly in another aspect, this invention concerns:

25 a method of management (by which is meant treatment or prophylaxis) of disease or conditions associated with GnRH, which comprises administering to a subject an effective amount of a compound of formula (I) above, or a pharmaceutically acceptable salt thereof; and

30 a compound of formula (I) for use in medicine, particularly in the management (by which is meant treatment or prophylaxis) of diseases or conditions associated with GnRH; and

the use of a compound of formula (I) in the preparation of an agent for the management (by which is meant treatment or prophylaxis) of diseases or conditions associated with GnRH.

5 Compounds of the invention may have utility in the treatment or prevention of cancer.

The term "cancer" as used herein refers to any disease or condition characterised by uncontrolled, abnormal growth of cells and includes all known types of cancer, for example cancer of the bladder, breast, colon, brain, bone, head, blood, eye, neck, skin, lungs, ovaries, prostate and rectum; digestive,
10 gastrointestinal, endometrial, hematological, AIDS-related, muscoskeletal, neurological and gynecological cancers; lymphomas, melanomas and leukemia.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation
15 intended for the oral administration of humans may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

Appropriate dosage levels may be determined by any suitable method known to one skilled in the art. It will be understood, however, that the specific
20 dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet time of administration, route of administration, rate of excretion, drug combination and the severity of the disease undergoing treatment.

25 In therapeutic use, the active compound may be administered orally, rectally, parenterally, by inhalation (pulmonary delivery), topically, ocularly, nasally, or to the buccal cavity. Oral administration is preferred. Thus, the therapeutic compositions of the present invention may take the form of any of the known pharmaceutical compositions for such methods of administration. The
30 compositions may be formulated in a manner known to those skilled in the art so as to give a controlled release, for example rapid release or sustained release, of the compounds of the present invention. Pharmaceutically acceptable carriers

suitable for use in such compositions are well known in the art. The compositions of the invention may contain 0.1-99% by weight of active compound. The compositions of the invention are generally prepared in unit dosage form. Preferably, a unit dose comprises the active ingredient in an amount of 1-500 mg. The excipients used in the preparation of these compositions are the excipients known in the art.

Appropriate dosage levels may be determined by any suitable method known to one skilled in the art. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the disease undergoing treatment.

Compositions for oral administration are preferred compositions of the invention and there are known pharmaceutical forms for such administration, for example tablets, capsules, granules, syrups and aqueous or oily suspensions. The pharmaceutical composition containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions, and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example corn starch or alginic acid; binding agents, for example starch gelatin, acacia, microcrystalline cellulose or polyvinyl pyrrolidone; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may

be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

5 Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

10 Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may
15 be a naturally occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long-chain aliphatic
—alcohols, for example heptadecaethyleneoxycetanol, or condensation products
of ethylene oxide with partial esters derived from fatty acids, for example
20 polyoxyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl or n-propyl p-hydroxybenzoate, one or more colouring agents, one or more flavouring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient
25 in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be
30 preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture

with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable sweetening, flavouring and colouring agents may also be present.

5 The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin, or mixtures of these. Suitable emulsifying agents may be naturally occurring gums, for example gum acacia or gum tragacanth, naturally occurring phosphatides, for example soya bean, lecithin, and esters or partial esters derived from fatty acids
10 and hexitol anhydrides, for example sorbitan monooleate and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example
15 glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavouring and colouring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending
20 agents which have been mentioned above. The sterile injectable preparation may also be in a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition,
25 sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid, find use in the preparation of injectables.

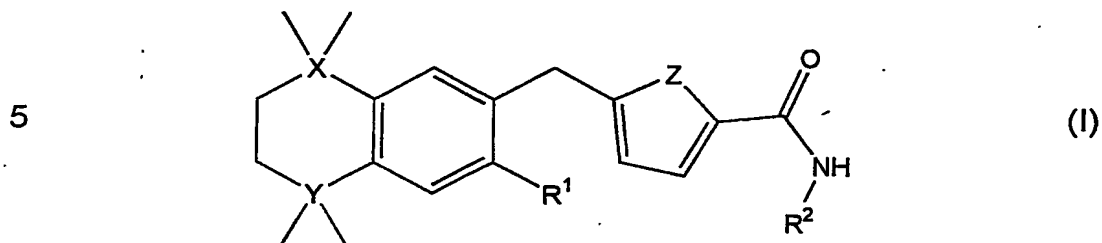
The compounds of the invention may also be administered in the form of
30 suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore

melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

5 Compositions for topical administration are also suitable for use in the invention. The pharmaceutically active compound may be dispersed in a pharmaceutically acceptable cream, ointment or gel. A suitable cream may be prepared by incorporating the active compound in a topical vehicle such as light liquid paraffin, dispersed in a aqueous medium using surfactants. An ointment may be prepared by mixing the active compound with a topical vehicle such as a mineral oil or wax. A gel may be prepared by mixing the active compound with
10 a topical vehicle comprising a gelling agent. Topically administrable compositions may also comprise a matrix in which the pharmaceutically active compounds of the present invention are dispersed so that the compounds are held in contact with the skin in order to administer the compounds transdermally.

CLAIMS

1. A compound of formula (I)



wherein

- 10 one of X and Y is Si and the other is C or Si;
 Z is NR, O or S and R is H or alkyl;
 R¹ is H, halogen, alkyl, alkenyl, alkynyl or cycloalkyl; and
 R² is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl,
 -alkyl-cycloalkyl, -alkyl-heterocycloalkyl, -alkyl-aryl or -alkyl-heteroaryl;
 15 or a pharmaceutically acceptable salt thereof.
2. A compound according to claim 1, wherein X and Y are each Si.
3. A compound according to claim 1 or claim 2, wherein R¹ is H or alkyl.
4. A compound according to claim 3, wherein R¹ is methyl.
5. A compound according to any preceding claim, wherein Z is O.
- 20 6. A compound according to any preceding claim, wherein R² is aryl, -CH₂-
 cycloalkyl, -CH₂-aryl, -CH₂-heterocycloalkyl or -CH₂-heteroaryl.
7. A compound according to claim 6, wherein R² is aryl.
8. A compound according to claim 1, which is *N*-(2,4,6-trimethoxyphenyl)-5-
 [3,5,5,8,8-pentamethyl-5,8-disila-5,6,7,8-tetrahydro-2-naphthyl)methyl]furan-2-
 25 carboxamide.
9. A pharmaceutical composition comprising a compound of any preceding
 claim and a pharmaceutically acceptable diluent or carrier, for use in therapy.
10. Use of a compound of any of claims 1 to 8, for the manufacture of a
 medicament for the treatment or prevention of a disease or condition associated
 30 with GnRH.
11. Use of a compound of any of claims 1 to 8, for the manufacture of a
 medicament for cancer therapy.

PCT Application
GB0305015

